Future and perspectives

Emerging Antibiotic Resistance Unit

Prof. Patrice Nordmann
Deaths Attributable to Antimicrobial Resistance Every Year by 2050

- **North America**: 317,000
- **Europe**: 390,000
- **Latin America**: 392,000
- **Africa**: 4,150,000
- **Asia**: 47,300,000
- **Oceania**: 22,000

Three irreversible resistance waves towards pandrug resistance in *Enterobacteriaceae*

- **1960-70**: Penicillinases
- **1980-2000**: ESBLs
- **2010....**: Carbapenemases
Three irreversible resistance waves towards pandrug resistance in *Enterobacteriaceae*

- **1960-70**
  - **Penicillinases**
  - 60-90%

- **1980-2000**
  - **ESBLs**
  - 5-80%

- **2010…**
  - **Carbapenemases**
  - 0.001-?%
CPE in Canada

- **KPC**
- **NDM**
- **OXA-48-like**
- **SME**
- **Other**

Year | Number of Isolates | (n) | Year | Number of Isolates | (n)
--- | --- | --- | --- | --- | ---
2008 | 5 | 5 | 2010 | 70 | 70
2009 | 4 | 4 | 2011 | 142 | 142
2012 | 150 | 150 | 2013 | 209 | 209
2014 | 320 | 320 | 2015 (6 months) | 204 | 204

Total (n=1102)

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France, 2004 – 2014,
March 14, 2014 (N = 913 [single isolates or clusters])

E. coli; 28%

N=913
France, 2014

n= 1,075

X 3 in 3 years

OXA-48 like 85.6%

NDM 8.5%

NDM + VIM 0.1%

NDM + VIM 0.1%

OXA-48-like + NDM 0.8%

IMI 0.3%

IMP 0.3%

VIM 2.7%

KPC 1.8%
France

E. coli

K. pneumoniae

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Spain

*E. coli*

*K. pneumoniae*
Germany

E. coli

K. pneumoniae
United Kingdom

E. coli

K. pneumoniae
United States

E. coli

K. pneumoniae
Future spread of carbapenemase in Enterobacteriaceae

OXA-48: *E. coli* ++, community-acquired, highly transferable plasmid
NDM: *Enterobacteriaceae*, community- and hospital-acquired
KPC; *K. pneumoniae*, hospital-acquired
OXA-48-like and NDM; the carbapenemase producers are spreading now in the community
Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014


Consecutive non-replicate clinical isolates (n=191) of carbapenem non-susceptible Enterobacteriaceae were collected from 21 hospital laboratories across Italy from November 2013 to April 2014 as part of the European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE) project. *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) represented 178 (93%) isolates with 76 (43%) respectively resistant to colistin, a key drug for treating carbapenemase-producing Enterobacteriaceae. KPC-KP colistin-resistant isolates were detected in all participating laboratories. This underscores a concerning evolution of colistin resistance in a setting of high KPC-KP endemicity.

Mortality rates are high due to limited treatment options, and some strains have the potential for rapid dissemination in healthcare settings [1,2]. In Europe, CRE have been reported from virtually all countries, but in some countries, namely Greece and Italy, they have spread rapidly and are presently endemic in many hospitals [3,4]. Resistance to carbapenems in Enterobacteriaceae is largely due to production of enzymes (carbapenemases) inactivating these antibiotics, hence the definition of carbapenemase-producing Enterobacteriaceae (CPE).

In Italy, the dramatic increase of carbapenem-resistant *Klebsiella pneumoniae* has been documented by the European Antimicrobial Resistance Surveillance Network (EARS-Net) and reported in the *Eurosurveillance* journal.
Carbapenemases in *Enterobacteriaceae*
Carbapenemases in *Enterobacteriaceae*
Carbapenemases in *Enterobacteriaceae*
A novel class A carbapenemase: FRI-1

Genetic and biochemical characterization of FRI-1 a carbapenem-hydrolyzing class A ß-lactamase from Enterobacter cloacae.

AAC, Oct. 2015
L. Dortet, L. Poirel, S. Abbas, S. Oueslati, P. Nordmann
THE POSSIBLE SOLUTIONS
Diagnostic tests are now available for detecting rapidly carbapenemases producers: let’s use it!!

Whole genome sequencing
The development of rapid point-of-care technologies is rapid.
Hygiene is now a worldwide concern
Future spread of carbapenemase in Enterobacteriaceae

OXA-48: *E. coli* **++, community-acquired, highly transferable plasmid

NDM: *Enterobacteriaceae*, community- and hospital-acquired

KPC; *K. pneumoniae*, hospital-acquired
### Antibiotics are in the pipeline, 2015

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
<th>ESBL</th>
<th>KPC</th>
<th>NDM-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane/tazobactam&lt;sup&gt;a&lt;/sup&gt;</td>
<td>On the US market</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ceftazidime/avibactam&lt;sup&gt;a&lt;/sup&gt;</td>
<td>On the US market</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Ceftaroline/avibactam&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Phase 2</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Imipenem/IMK 7655&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Phase 2</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Plazomicin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Phase 2</td>
<td>+</td>
<td>+</td>
<td>? /-</td>
</tr>
<tr>
<td>Enavocycline&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Phase 2</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Brilacidin&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Phase 3</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

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- **a.** β-Lactamase inhibitor
- **b.** Aminoglycoside
- **c.** Fluorocycline (targets ribosome)
- **d.** Peptide defense protein mimetic

WT = Wild type
ESBL = Extended spectrum β-lactamase
KPC = *Klebsiella pneumoniae* carbapenemase
NDM-1 = New Delhi metallo-β-lactamase

Adapted from NW Forscher, OD, 2013; 56(12): 18685-94
ACHN-978 is Effective vs. Ribosomal Methylose

Activity of ACHN-978 vs. NDM-1 Producing Strains
CDC Strain Collection (n=3)

<table>
<thead>
<tr>
<th>Agent</th>
<th>K. pneumoniae</th>
<th>E. coli</th>
<th>E. cloacae</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHN-978</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&gt;84</td>
<td>&gt;84</td>
<td>&gt;84</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;84</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;84</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;16</td>
<td>4</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;16</td>
<td>16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>4</td>
<td>0.25</td>
<td>4</td>
</tr>
</tbody>
</table>

- armA (n=14), rmtB (n=8) and rmtD (n=1) represented
- A. baumannii (n=4), Klebsiella spp. (n=7), E. coli (n=4), Enterobacter cloacae (n=6), Serratia marcescens (n=2), Citrobacter freundii (n=1), Proteus mirabilis (n=1)
- ACHN-978 active vs. isolates expressing 7 different methylases, armA and rmtA – F, from the UK Health Protection Agency

ACHN-978: Activity vs. Methylase-Expressing Strains (n=25)
Impact of the New Delhi metallo-beta-lactamase on beta-lactam antibiotics

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Abstract: Since the first New Delhi metallo-beta-lactamase (NDM) report in 2009, NDM has spread globally causing various types of infections. NDM-positive organisms produce in vitro resistance phenotypes to carbapenems and many other antimicrobials. It is thus surprising that the literature examining clinical experiences with NDM does not report corresponding poor clinical outcomes. There are many instances where good clinical outcomes are described, despite a mismatch between administered antimicrobials and resistant in vitro susceptibilities. Available in vitro data for either monotherapy or combination therapy does not provide an explanation for these observations. However, animal studies do begin to shed more light on this phenomenon. They imply that the in vivo expression of NDM may not confer clinical resistance to all cephalosporin and carbapenem antibiotics as predicted by in vitro testing but other resistance mechanisms need to be present to generate a resistant phenotype. As such, previously abandoned therapies, particularly carbapenems and beta-lactamase inhibitor combinations, may retain utility against infections caused by NDM producers.

Keywords: carbapenemase, metallo-beta-lactamase, resistance
Non-conventional therapy
“My approach is nontraditional, but from a uniquely Western perspective.”
Phage therapy is the use of lytic phages for treating bacterial infections.
Phage therapy: advantages

Narrow spectrum
- no effect on commensal microflora
- no cross-resistance effects
- flexible: cocktail spectrum may be adapted to the clinical needs
treatment can be customized. A personalized medicine!

Different kinetics
- in theory a single dose may be sufficient for treating an infection
- less dependant on bloodstream: phages go through also BBB
- phage transfer to other individuals may be possible: prophylactic effect

No relation with antibiotic resistance: MDR bacteria can be treated.
Disadvantages of phage therapy

- Bacterial specificity
- Variable activity depending on the physiological situation of the Bacteria
- Need to know the bacterial isolate; narrow spectrum
- Reproducibility of the batches
- Lysogeny?
- Complex pharmacokinetics
- Potential neutralization by the host immune response
- Difficult purification
“Voici maintenant venir de moindres personnages de la troupe microbienne ; mais dans les bonnes compagnies, il n’est pas de rôle qui ne fournisse une carrière à celui qui sait le faire valoir”